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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/185,807	11/04/98	LEUNG	S 018733/0875

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EXAMINER	
HELMS, L	
ART UNIT	**PAPER NUMBER**
1642	13

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Please find below and/or attached an Office communication concerning this application or pr ceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/185,607	Applicant(s) Leung et al
	Examiner Larry R. Helms Ph.D.	Group Art Unit 1642

☒ Responsive to communication(s) filed on *27 Oct 2000*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-37* is/are pending in the applicat

Of the above, claim(s) *15, 28, and 30-37* is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-14, 16-27, and 29* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☒ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *4 and 5*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Applicant's election of Group I and the species DOTA-bearing peptides in Paper No. 12 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). The claims that read on the elected invention are claims 1-14, 16-27, and 29.

2. Claims 15, 28, and 30-37 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions. Election was made **without** traverse in Paper No. 12.

3. Claims 1-14, 16-27, and 29 are under examination.

Specification

4. The disclosure is objected to because of the following informalities:

a. The first line of the application should indicate that this application is claiming benefit to provisional application 60/064,386, filed 11/06/97.

b. The specification should be updated to indicate the current status of all U.S. Applications, for example on page 13, line 21, application 08/731,107 is now U.S. Patent 5,965,131.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-14, 16-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-14, 16-18 are indefinite for reciting incomplete method claims in claims 1, 6, 8, and 16 which do not clearly set forth method steps and does not include a resolution step which reads back on the preamble of the claimed method. Merely expressing a cell with a vector encoding an antibody having a glycosylated site in a medium with a ketone derivative in claims 1 and 6 or adding a reaction with an agent as recited in claims 8 and 16 does not result in a method of producing an antibody or an immunoconjugate. The claims should conclude with a step of producing a glycosylated antibody or immunoconjugate as required by the preamble, which recites "a method of making a glycosylated antibody" or "a method of making an immunoconjugate".

b. Claims 1, 3-14, 16-18 are indefinite for reciting "ketone derivative of a saccharide or saccharide precursor" in claims 1, 6, 8, 16 because the exact meaning of the phrase is not clear.

It is not clear how the "ketone derivative" is to be modified to result in a "derivative". The term "derivative" is not one which has a universally accepted meaning in the art nor is it one which has been adequately defined in the specification. The primary deficiency in the use of this phrase is the absence of a ascertainable meaning for said phrase. Since it is unclear how the "saccharide precursor" are to be derivatized or what a ketone derivative is in order to yield the class of derivatives referred to in the claims, there is no way for a person of skill in the art to ascribe a discrete and identifiable class of compounds to said phrase. Moreover, does the phrase "ketone derivative" mean an aldehyde? In addition, since the term "derivative" does not appear to be clearly defined in the specification, and the term can encompass many types of molecules. In addition, it is not clear what is meant by "saccharide precursor". Does the phrase mean a molecule that can be used in the biosynthetic pathway to a saccharide such as starch, carbon atoms, etc? In absence of a single defined art recognized meaning for the phrases and lacking a definition of the terms in the specification, one of skill in the art could not determine the metes and bounds of the claims.

D c. Claims 14 and 27 are indefinite for reciting the abbreviation "DOTA". Full terminology should be in first instance of the claims followed by the abbreviation in parentheses. Dependent claims may then use the abbreviation. Abbreviations render the claim indefinite because the same abbreviation may represent more than one element or concept.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-14, 16-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of making a glycosylated antibody or immunoconjugate comprising hLL2 having a reactive ketone group on the glycosylated site in HCN1, HCN5, and position 18 in the Vkappa, wherein the expressed antibody is expressed in SP2/0 cells in a culture medium comprising N-levulinoyl mannosamine or N-levulinoyl frucose wherein the antibody is an antigen binding fragment and the antibody is reacted with an agent comprising a ketone-reactive group, does not reasonably provide enablement for a method of making a N-linked or O-linked glycosylated antibody or immunoconjugate in any cell having a reactive ketone group at any position in the antibody other than those recited above or using any ketone other than those listed above. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to a method of making a N-linked or O-linked glycosylated antibody or immunoconjugate having a reactive ketone group on any glycosylation site in any antibody comprising expression of the vector encoding the antibody in any cell with any ketone of a saccharide.

The specification teaches a method of making a glycosylated antibody of hLL2 glycosylated at residue 18 in the Vkappa and HCN-1 and HCN-5 in CH1 (see example 1 and 2). The specification indicates that a ketone handle can be introduced by incorporating FucLev into engineered CHOs (see page 18, lines 5-15). The specification contemplates that adding ManLev to a culture of SP2/0 cells that contains the expression vector hLL2pdHL2(HCN1/5) results in the formation of reactive ketone groups on the glycosylated sites (see page 19, example 5). The specification teaches that mutants that were designed to contain a glycosylation site in the constant light chain region (KCN1-5) were not glycosylated (see page 16, lines 13-15). The specification fails to enable any other N-linked glycosylation sites other than those above or in any other antibody. The specification fails to enable any O-linked glycosylation or glycosylation in any other cell except SP2/0.

The claims are not commensurate in scope with the enablement provided in the specification. The claims broadly encompass a N or O-linked glycosylation site anywhere in the antibody, however, the specification fails to enable a glycosylation site that is glycosylated at positions other than those of HCN1 or HCN5 in the CH1 domain or position 18 in the Vkappa. The claims also broadly encompass expression of the antibodies in any cell that allows

glycosylation. As evidenced by Wright et al (Springer Semin Immunopathology 1993 Vol 15 :259-273), the glycosylation of the Vh chain "contributes to alterations in protein stability, leading to the formation of immune complexes or tissue deposition" and Wright et al further caution that "disruption in the regulation of glycosylation can lead to the expression of altered carbohydrate structure (such as galactosyl sugars) with a resulting glycoproteins exhibit properties (such as a tendency towards aggregation) that contribute to disease" (page 270, second to last paragraph). Moreover, Wright et al teach while N-linked glycosylation is a wide spread post translational modification, occurring among mammalian, yeast, insect and plant cells, "the processing steps in the Golgi apparatus vary among cell types". (Page 259, second paragraph). Wright documents that plant cells use xylose, mammalian cells use sialic acid, and yeast add many mannose monomers than mammalian cells. Also insect cells do not appear to process the carbohydrates beyond the Man3 GLC Nac2 step. Accordingly, one skilled in the art would reasonably conclude that the tertiary structure of glycosylated antibodies expressed in the various eukaryotic hosts encompassed by the broadly written claims would differ, based upon the teachings of Wright et al.

Further, Wright et al specifically teach that "the position of the carbohydrate addition appears to influence the structure of the added carbohydrate" (page 269, first full paragraph) and that "glycosylation can induce structural abnormalities in the light chain that lead to tissue deposition" (page 266-267, bridging paragraph). Further, Wright et al go on to teach that "many Vh3 genes ... contain potential N-linked glycosylation sites as ASN 72, in FR3, although it has

not yet been determined whether any of these sites are in fact glycosylated". Finally, Wright et al teach that the sugars may fill "pockets" within the immunoglobulin , thus one of ordinary skill in the art would reasonably conclude that addition of carbohydrates to an antibody would alter the tertiary structure, as taught in general by Delente (Trends in Biotechnology 3, 1985). Thus Wright et al teach the unpredictability of adding a glycosylation site to an antibody molecule, specifically that some additions result in protein aggregation that the position of the addition is important for determining whether the glycosylation site is in fact recognized by the cell, and once glycosylated, whether the antibody is more or less stable and binds antigen like the unaltered form. One skilled in the art would also reasonably conclude from Wright et al that glycosylation in the CH1 or Vkappa region could have similar structural effects as those in the light chain mentioned above. Moreover, the specification teaches that sites at KCN1-5 were not glycosylated (see page 16, lines 13-15).

As evidenced by Olden et al (Biochem et Biophys Acta Vol 650 1982 209-232), carbohydrate structures are a form of sorting signals used by the cells and that O-linked glycosylation differ from N-linked glycosylation due to the sugars which are added to each type during protein processing. O-linked carbohydrates use galNAC while N-linked carbohydrates use GlcNAC (see page 225, second column, first paragraph). Olden teaches that O-linked carbohydrates differ in tertiary structure from N-linked carbohydrates and therefore, one skilled in the art would reasonably conclude that antibodies possessing O-linked sugars would also differ in their tertiary structure from those antibodies expressing N-linked sugars.

Moreover, while the N-linked carbohydrate addition site is specifically the sequence "ASP-X-SER/THR, where X may stand for any amino acid, the O-linked addition site is less defined as only a serine or a threonine residue. Carbohydrate moieties are not attached to all lumenal serine or threonine residues and it would be unpredictable to determine at which lumenal positions a serine or a threonine could be placed within the antibody molecule so that the serine or threonine would be glycosylated. Once glycosylated, whether by the N-linked or O-linked mechanism, it would require undue experimentation to determine whether the antibody expression, stability, tertiary structure or affinity had been affected.

Therefore, in view of the lack of guidance in the specification and in view of the unpredictability in the art of glycosylation of proteins in general as evidenced by, Wright et al, Dalente, and Olden et al and the unpredictability of glycosylation of antibodies as evidenced by the specification, one of skill in the art would be forced into undue experimentation in order to practice the broadly claimed invention.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 19, 21-22, 24-26, and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by Sivam et al (WO 90/03401, published 4/5/90, IDS #5).

a. The claims recite a glycosylated antibody or antigen binding antibody fragment having a reactive ketone group on one or more glycosylated site, an imunoconjugate wherein the diagnostic agent is an imaging radioisotope and conjugated through the glycosylation site and an immunoconjugate wherein the agent is chelated to the diagnostic radioisotope.

b. Sivam et al teach a glyosylated antibody and immunoconjugates wherein a number of glycosylation sites have a reactive ketone group (see page 2-3) and the agent is a imaging radioisotope (see page 21) and a chelating ligand plus agent or radionuclide (see page 21, lines 7-10).

11. Claims 22-26 are rejected under 35 U.S.C. 102(b) as being anticipated by Leung et al (J. Of Immunology 154:5919-5926, 1995, IDS #5).

a. Claims 22-26 have been described supra. Claim 23 recites wherein the glycosylated site is in the Vkappa domain.

b. Leung et al teach an immunoconjugate comprising a glycosylated antibody at site 18 of Vkappa and a conjugate to 90Y (see abstract).

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 19-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sivam et al (WO 90/03401) and further in view of Hansen et al (U.S. Patent 5,443,953, issued 8/22/95).

a. Claims 19 and 21 have been described supra. Claim 20 recites wherein the antibody is glycosylated in the Vkappa domain.

b. Sivam et al has been described supra. Sivam et al does not teach glycosylation in the Vkappa domain. This deficiency is made up for in the teachings of Hansen et al.

c. Hansen et al teach a glycosylated antibody and an immunoconjugates wherein the antibody has a glycosiylated site at positions 18-0 in the Vkappa domain and the immunoconjugates ate conjugated by through the carbohydrate. Hansen et al also teach it is possible to introduce mor than one glycosylation site at other positions (see column 10, lines 20-27).

d. It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have used the antibody of Hansen et al and the method of Sivam et al to produce the glycosylated antibody and immunoconjugates with a reactive ketone group on the glycosylated site.

e. One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success in using the antibody of Hansen et al and the method of Sivam et al to produce the glycosylated antibody and immunoconjugates with a reactive ketone group on the glycosylated site because Sivam et al teach a glycosylated antibody which can contain more than one glycosylation site which contains a reactive ketone on the glycosylation site. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success in using the antibody of Hansen et al and the method of Sivam et al to produce the

glycosylated antibody and immunoconjugates with a reactive ketone group on the glycosylated site because Hansen et al teach an antibody that is glycosylated in the Vkappa domain and inmmunoconjugates thereof and Hansen et al teach that the glycosylation site can be at alternative positions. In addition, it would have been obvious to use the antibody of Hansen et al and the method of Sivam et al to produce the glycosylated antibody and immunoconjugates with a reactive ketone group on the glycosylated site because other sites in the antibody could be used with the method of Sivam et al.

f. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

15. Claims 22-25 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sivam et al (WO 90/03401) as applied to claims 22 and 25 above, and further in view of Li et al (Bioconjugate chem. 4:275-283, 1993).

a. Claims 22 and 25 have been described supra. Claim 27 recites wherein the agent is a DOTA-bearing peptide.

b. Sivam et al has been described supra. Sivam et al also teach various chemistries for conjugation. Sivam et al does not teach a DOTA-peptide conjugated to the antibody. This deficiency is made up in the teachings of Li et al.

c. Li et al teach a DOTA-peptide conjugated to an antibody.

d. It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have used the method of Sivam et al and conjugate a DOTA-peptide as taught by Li et al to the glycosylation site.

e. One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success in using the method of Sivam et al and conjugate a DOTA-peptide as taught by Li et al to the glycosylation site because Sivam et al teach a glycosylated antibody which can contain more than one glycosylation site which contains a reactive ketone on the glycosylation site. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success in using the method of Sivam et al and conjugate a DOTA-peptide as taught by Li et al to the glycosylation site because Li et al teach the radiolabeled conjugates are kinetically inert and can be conjugated to an antibody (see abstract). In addition, it would have been obvious to use the DOTA-peptide as a conjugate for a chelate for radioisotopes as taught by Li et al and conjugate the DOTA-peptide through the glycosylation site because Sivam et al teach various chemistries for conjugation to a reactive ketone.

f. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Double Patenting

16. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

17. Claims 22-26 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5 of U.S. Patent No. 5,443,953. Although the conflicting claims are not identical, they are not patentably distinct from each other. The claims in the instant application are broader in scope than those in 5,443,953. The instant claims recite an immunoconjugate wherein the glycosylation site is at Vkappa domain and an agent comprising a chelating agent or peptides. The claims in 5,443,953 recite an immunoconjugate that is glycosylated in position about 18 in of the light chain and conjugates of chelators and polypeptides. It would have been obvious to glycosylate in the Vkappa domain in view of the 5,443,953 patent claims which are drawn to glycosylation at position about 18 in the Vkappa and immunoconjugates thereof.

Conclusions

18. No Claims are allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

20. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879

Sheela J. Huff

SHEELA HUFF
PRIMARY EXAMINER